BRMAC Meeting 32, May 10, 2002
Draft Questions for Committee Discussion

1. If vector sequences are detected in the motile sperm fraction of clinical trial subjects, the FDA's current approach is to suspend accrual to the study pending additional data regarding the persistence of the vector. Enrollment has been allowed to proceed when there are data to show that the vector does not persist (three consecutive samples test negative).

    A. Does the committee agree that a clinical hold is warranted when motile sperm tests positive for vector sequence, or should enrollment be allowed to continue with appropriate modification made to consent documents?

    B. Please discuss the implications of detecting vector sequences due to the presence of contaminating transduced PBMC or vector (either free or on the surface of a sperm) in the motile sperm fraction.

2. There are technical limitations in the ability to monitor women and certain men for evidence of germline alterations. One approach to monitoring subjects for germline alteration would be to restrict early clinical development of certain gene transfer products to subjects who have been shown to be capable of repetitively supplying adequate semen samples for analysis in order to collect data regarding distribution of the vector to germline tissues and the persistence of vector. Depending on the amount of data required, much of the early clinical experience with the vector might be limited to this restricted population. A development program requiring extensive characterization of distribution to germline cells and germline alterations might substantially delay acquisition of adequate safety and efficacy data in other populations (e.g., women).

    Please discuss those situations in which clinical development of a gene transfer agent might proceed in the absence of the ability to monitor semen for evidence of germline alterations or the presence of vector gene sequences.

3. Given a situation where vector sequences are persistently, not transiently, detected in the motile sperm fraction of clinical trial subjects please discuss what regulatory actions would be appropriate for the FDA to take. Should these trials proceed with appropriate modifications made to consent documents? Should further studies be limited to subject populations that are unable to reproduce?